REMARKS

Claims 1-13 are currently pending. Claim 7 is withdrawn.

Claim 1 is amended herein to remove the language "and a protective foil or sheet to be removed prior to use".

No new matter is introduced by this amendment and no change in inventorship is a result of this amendment.

RESPONSE TO OFFICE ACTION DATED 6 JANUARY 2010

Applicant appreciates the courtesy shown by Examiner Buckley and her Supervisor in the telephone interview on 18 May 2010. The following response takes account of that discussion.

1. Rejection under 35 U.S.C. §103(a)

Claims 1–6 and 8–13 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over D'Angelo & Schur (U.S. Patent No. 5,932,240, herein "D'Angelo") in view of Lauterbach *et al.* (U.S. Patent Application Publication No. 2003/0027793, herein "Lauterbach").

No admission is made herein that Lauterbach (mis-spelled "Lauterback" in the published application) constitutes prior art to the present invention. Although the Examiner notes that Lauterbach has an earlier effective U.S. filing date for 102(e) purposes (12 March 2002) than the present application, it is noted that Lauterbach is not statutory prior art against the present invention, having published after the priority date of the present application. Applicant reserves the right to disqualify this publication as prior art; however, the question is moot. As shown below, even if Lauterbach were available as prior art, a *prima facie* presumption of obviousness has not been established over D'Angelo in view of Lauterbach.

Pending Claim 1 recites: A transdermal delivery system (TDS) comprising a backing layer and a self-adhesive matrix containing rotigotine, wherein the self-adhesive matrix comprises a solid or semi-solid semi-permeable polymer

(1) wherein rotigotine in its free base form is incorporated,

(2) which comprises a multitude of microreservoirs within the matrix, said microreservoirs containing rotigotine,

(3) which is permeable to the free base of rotigotine,

(4) which is substantially impermeable to the protonated form of rotigotine, and

(5) wherein the microreservoirs have a maximum diameter that is less than the thickness of the matrix;

and wherein the backing layer is inert to the components of the matrix.

The Examiner maintains that it would have allegedly been obvious to "combine the teaching of D'Angelo…and Lauterbach…by adding rotigotine free base to the microreservoir component of the transdermal formulation taught by D'Angelo…to provide mulitple unit doses of rotigotine." (6 Jan 2010 Office Action, p. 6). This rejection is respectfully traversed.

Applicant maintains all arguments presented in the response dated 24 Sept 2009 and supplements the 24 Sept 2009 response as follows. Claim 1 and claims depending therefrom are non-obvious over D'Angelo and Lauterbach for at least the following reasons:

A. <u>Key Differences Between Applicant's Patch and D'Angelo's Patch:</u>

The Examiner states that D'Angelo "does not teach the specific instantly claimed compound [rotigotine] or silicone pressure adhesive [note not an element of Claim 1]. *See* 6 Jan 2010 Office Action, p. 5, 2nd paragraph. However, as discussed below, there are many more features of Applicant's patch that are not taught or suggested by D'Angelo.

At the outset, Applicant's patch is very different from D'Angelo's patch. Applicant's non-segregated patch has a self-adhesive matrix (polymer) that contains rotigotine-containing microreservoirs within the self-adhesive polymer. Applicant's microrservoirs are very small (not visible to naked eye) and have a diameter less than the thickness of the matrix. The self-adhesive polymer is permeable to rotigotine free base and substantially impermeable to rotigotine in protonated form. This intriguing quality of the self-adhesive polymer with rotigotine allows the matrix to be put directly on the subject's skin and a high-steady state flux of rotigotine will transfer from the polymer to and through the skin of the patient. One can envision this patch with just a backing layer and a self-adhesive polymer on top that is put on the skin and will stay in place because the polymer itself is self-adhesive. Nothing further is

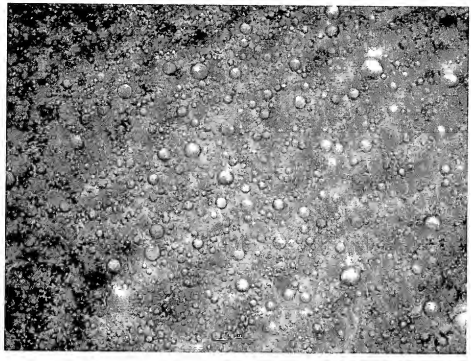
required by the patient for the drug to release to the skin of the patient.

Unlike Applicant's non-segregated patch, D'Angelo's patch has "multiple unit dose reservoirs with each reservoir having individual tear-and-release or pull-and-release resealable closure means for initiation and administration of medication." *See* attached argument and characterization presented by D'Angelo for the EP counterpart case of D'Angelo, EP0593746B1 at p. 2. During European prosecution, D'Angelo differentiates the prior art by explaining that, unlike the prior art, D'Angelo's multidose patch assembly can be individually triggered by the patient.

Applicant will now demonstrate key differences between Applicant's patch and D'Angelo's patch in more detail below:

a. Applicant's microreservoirs vs. D'Angelo's microspheres

   i. **Applicant's microreservoirs** are defined on p. 6 of the application as filed as "particulate, spatially and functionally separate compartments consisting of pure drug or a mixture of drug and crystallization inhibitor, which are dispersed in the self-adhesive (polymer) matrix." Preferably the self-adhesive matrix contains 10^3 to 10^9 microreservoirs per cm^2 of its surface. A microscopic picture of the microreservoirs are shown in Fig. 5:



ii. **D'Angelo claims "microspheres"** in Claim 1. Microspheres are reported at Col. 4 in D'Angelo: "the unit doses [within the individual reservoirs] being in the form of a multiphase composition of microspheres wherein an internal phase comprises the drug actives and adjuvants surrounded by an outer phase of film-forming polysaccarides engrafted with transdermal promoters..." (emphasis added) *See also* U.S. prosecution history of D'Angelo, Office Action dated 18 Aug 1998 and Response dated 14 Dec 1998 where D'Angelo amended the language of Claim 18 to clarify that their composition is multiphase in response to the Examiner's Sec. 112 rejection (attached hereto). Applicant's microreservoirs do not have this multiphase composition as described by D'Angelo. Applicant's microreservoirs have either (1) pure drug or (2) drug and crystallization inhibitor. Applicant' microreservoirs are not the same as D'Angelo's microspheres.

b. Activation mechanism of Applicant's microreservoirs vs. D'Angelo's microspheres

   i. D'Angelo states at Col. 4: "...the microspheres being distributed through a diffusable matrix for the composition; the individual seal means having means for disrupting the microspheres upon activation of the seal means to release the drug actives and adjuvants in the unit dose compartment to diffuse through the matrix to a patient's skin." (emphasis added) In fact, in prosecution of the EP counterpart case, D'Angelo states: "It is important to note, that the present invention is defined as a multidose system wherein it is possible to trigger individual doses of drugs after the patch has been placed on the patient's skin. The release of the drugs is effected when individual taps, sliders or similar devices are removed and a portion of the drug active is thereby ruptured when the microspheres are broken." (emphasis added)

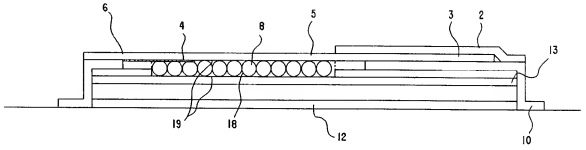
   ii. Applicant's microreservoirs are not "disrupted" or "activated" or "broken" by any means, including a tear-and-release or pull-and-release mechanism.

c. Placement in the patch of Applicant's microreservoirs vs. D'Angelo's microspheres

   i. As claimed in Claim 1, Applicant's microreservoirs are within the self-adhesive matrix (polymer) such that their diameter is smaller than the thickness of the matrix.

   ii. When discussing D'Angelo, the Examiner states on p. 10 of the current OA: "It is noted that the microreservoirs are situated within the structure of the matrix (see D'Angelo Figure 2) as required by instant claim 1." First, D'Angelo does not report Applicant's "microreservoirs". Second, although D'Angelo's microspheres are shown "within" the matrix, D'Angelo's microspheres have to be in

contact with the edge of the matrix. As noted above, D'Angelo's microspheres are ruptured upon activation of the seal means. In order for the microspheres to be ruptured, they have to at least be touching the edge of the matrix or else they won't be able to be ruptured and then have the drug transfer to the skin. This can be seen in D'Angelo's only figure.



In contrast to D'Angelo, Applicant wants to avoid direct contact between the skin and the microreservoirs containing rotigotine. The reason is that the skin has a slightly acidic pH and direct contact between the skin and Applicant's microreservoirs in the matrix leads to protonation of rotigotine, thereby deteriorating the semi-permability of the matrix.

iii. **Thus, although D'Angelo claims (Claim 1) "microspheres being distributed through a diffusable matrix", D'Angelo's microspheres are not within the matrix such that their diameter is smaller than the matrix and avoids contact with the skin surface.**

d. Applicant's self-adhesive matrix vs. D'Angelo's non-adhesive hydro-matrix

i. Applicant's patch uses a self-adhesive matrix (polymer), as claimed in Claim 1. As noted above, the rotigotine-containing microreservoirs are within this self-adhesive matrix (polymer).

ii. D'Angelo's multi-dose patch uses a non-adhesive polymer. This means that, unlike Applicant, D'Angelo uses a separate adhesive (3M Cotran® 9872) to attach D'Angelo's multi-dose system to a patient's skin.

iii. Further, D'Angelo reports that they use a gel matrix, preferably a hydrogel matrix. *See* Col. 6, lines 42-55. As noted in Applicant's 24 Sept 2009 response, D'Angelo's hydrogel matrix likely contains enough water that would produce the salt form of rotigotine. Thus, even if one could put rotigotine in D'Angelo's patch, D'Angelo's matrix would likely be permeable to the salt (protonated) form of rotigotine and thus not work (and be counter to Applicant's Claim 1).

e. Property of Applicant's self-adhesive matrix vs. D'Angelo's non-adhesive matrix

i. Applicant's self-adhesive matrix is surprisingly permeable to the free base of rotigotine and substantially impermeable to rotigotine in protonated form.

ii. D'Angelo does not mention rotigotine nor does D'Angelo mention any of these types of characteristics for a drug used in their patch, e.g. insulin.

Thus, one can see that D'Angelo's multi-unit dose patch system is very different from Applicant's patch. Lauterbach is only relied on for the rotigotine element of Claim 1. Contrary to the Examiner's assertion that "the cited art teaches all of the instant claimed limitations" at p. 7 of the 6 Jan 2010 Office Action, neither D'Angelo nor Lauterbach teach or suggest:

(1) Microreservoirs, as defined by Applicant, containing rotigotine or rotigotine plus crystalization inhibitor; and

(2) Microreservoirs within the matrix, and

(3) Microreservoirs having a maximum diameter less than the thickness of the matirix; and

(4) A matrix permeable to rotigotine free base; and

(5) Impermeable to rotigotine in protonated form.

For at least this reason, a presumption of *prima facie* obviousness has not been established for Claim 1 in view of D'Angelo and Lauterbach.

B. No Reason to Modify D'Angelo/Lauterbach to Arrive at Applicant's Invention

Further, there is no motivation to modify D'Angelo to includes items (1) – (5) listed above.

(1) As noted in Applicant's 24 Sept 2009 response, D'Angelo's patch would not work if modified to be like Applicant's patch. If the ordinary artisan changed the size of D'Angelo's microspheres they would not be able to be ruptured and release to the skin. Thus, this modification to D'Angelo would change the principle operation of D'Angelo's patch and yield a patch unsatisfactory for its intended utility (utility is discussed below).

(2) The Examiner asserts in the 6 Jan 2010 Office Action on p.7, that "it would be within the scope of skill and knowledge of an artisan skilled in the art to manipulate the size of the microreservoirs…because this is routine in the pharmaceutical art." This conclusion is (1) erroneous and (2) not supported by any evidence of record. Applicant's claimed invention is not a mere manipulation or modification of the size of D'Angelo's microspheres. First, as shown above, Applicant's microreservoirs are not the same as D'Angelo's microspheres. Second, Applicant discovered that they needed to decrease the size of their microreservoirs because the larger size and/or amount of drug salt residues in the patch led to slower initial drug release. Whereas, if you decrease D'Angelo's microspheres, D'Angelo's patch will not work. Third, Applicant's claimed invention involves more than the size of Applicant's microreservoirs. This is at least demonstrated by all of the elements of Applicant's Claim 1, for example the permeability of Applicant's self-adhesive matrix, and the differences set forth above between D'Angelo's patch and Applicant's patch.

For at least this reason, a presumption of *prima facie* obviousness has not been established for Claim 1 in view of D'Angelo and Lauterbach.

C. Utility of D'Angelo's patch teaches away from Utility of Applicant's Patch

The utility of Applicant's patch is to control the transport of rotigotine toward and across the skin, thereby enhancing the flux of rotigotine across the patch/skin interface. Applicant's patch provides a non-segregated dose of rotigotine to a patient.

In contrast, D'Angelo's patch is not designed to provide enhanced delivery of rotigotine. D'Angelo's utility is to provide a patch that allows patients to self-administer multiple doses of drug, such as insulin, by tearing off strips on individual dose reservoirs. D'Angelo states: "The principle of single unit doses in the multiple dose assembly is particularly useful as only a limited amount of the drug actives is exposed to the skin for transdermal absorption. When non-segregated muliple doses, as taught by the prior art are used, there arise problems." *See* Col. 5, lines 18-23, emphasis added. Therefore, D'Angelo actually teaches away from Applicant's patch which is non-segregated (*i.e.* Applicant's patch does not have discrete unit dose reservoirs).

D. Not Obvious to Put Rotigotine Within a Self-Adhesive Matrix

When formulating a *prima facie* case of obviousness, a reasonable expectation or predictability of success is required, as noted in MPEP § 2143.02: "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art." And see *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143, 148 (C.C.P.A. 1976) (stating that there must be a showing of a reasonable expectation of success and the alleged combination cannot be said to be "inherently" successful).

It was difficult and not obvious to put rotigotine within a self-adhesive matrix, and have the matrix be permeable to rotigotine free base and substantially impermeable to the protonated form of rotigotine for at least the reasons below:

(1) **Matrix Permeability**: No guidance is provided by the alleged combination or the general art to make a self-adhesive matrix permeable to the free base of rotigotine and substantially impermeable to the protonated form of rotigotine, as found in instant Claim 1. Too much water content in the matrix causes the

protonated form of rotigotine to be formed. Protonated rotigotine can not be released from the matrix. Thus, for example, the hydrogel matrix 18 of D'Angelo likely contains enough water to produce the salt form of rotigotine. Therefore, D'Angelo's patch has a matrix that is likely permeable, not impermeable, to the protonated form of rotigotine.

(2) **High-steady state flux**: No guidance exists to suggest to the ordinary artisan that rotigotine could be transferred to the skin and provide a high-steady state flux of rotigotine in the claimed microreservoir matrix. D'Angelo uses a physical means (tearing off) to disrupt and release the drug active from D'Angelo's microspheres, so D'Angelo certainly provides no motivation on how to make a rotigotine patch which can provide enhanced delivery by being permeable to rotigotine free base and substantially impermeable to protonated rotigotine.

(3) **Back diffusion and rotigotine delivery**: Further, Applicant's patch overcame the difficulty of preventing back diffusion of the rotigotine drug portion which is ionized in the skin according to its pKa value – from the skin tissue into the TDS, and offering substantially continuous delivery of the active compound across the stratum cornea not only via the more common lipophilic route (e.g. intercellular) but also through hydrophilic pores (e.g. eccrine sweat glands). *See* specification as filed at p. 2- p. 3.

(4) **Skin barrier**: The skin is a very efficient barrier for most drug candidates. Membrane controlled systems are more or less limited in practice to transdermal delivery of active substances that reveal a very high skin permeability. Additionally, special requirements on drug kinetics have to be met like contact delivery over several days. *See* specification as filed at p. 2.

Thus, as illustrated above, it was not obvious from the alleged combination of D'Angelo and Lauterbach or the art in general that enhanced delivery of rotigotine could be established by putting rotigotine-containing microreservoirs within a self-adhesive matrix. D'Angelo and Lauterbach fail to provide any reasonable expectation of success with respect

to Claim 1, and therefore cannot be used to establish a *prima facie* presumption of obviousness.

2. Provisional Obviousness-Type Double patenting over Serial No. 10/627,990 in view of D'Angelo and Lauterbach

Claims 1–6 and 8–13 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over Claims 1–13 of copending application Serial No. 10/627,990, in view of D'Angelo and Lauterbach. This rejection is provisional because the allegedly conflicting claims have not yet been patented.

The present rejection is respectfully traversed, at least for the reason that the present application has an earlier filing date (22 July 2003) than the reference application (July 28, 2003), and therefore, when issued as a patent, will expire before any patent that issues from the reference application. Rejection for double patenting is warranted only where "issuance of a second patent would provide unjustified extension of the term of the right to exclude granted by a patent" (MPEP 804.II.*B*.1). That is not the case here.

Applicant notes that a terminal disclaimer was filed in the '990 application on 29 July 2008.

3. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated or rendered moot herein. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Action and that the Application is in condition for allowance.

If personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number below.

Respectfully submitted,

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